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Prostaglandins and Cyclic Nucleotides in the Chédiak-Higashi Syndrome and Experimental Systemic Lupus Erythematosus

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Prostaglandins and cyclic nucleotides are important regulators of cell function and immune/inflammatory responses. Chédiak-Higashi (CH) syndrome in man is a genetic disorder characterized by pale skin, hair, and eye color, abnormal lysosomes, and recurrent infections. Oculocutaneous pigment dilution and impaired leukocyte function appear to be due to a defect in microtubule assembly. Whereas human peripheral blood polymorphonuclear (PMN) leukocytes do not form surface caps with concanavalin A (Con A) except after treatment with agents such as colchicine that inhibit microtubule assembly, CH PMN leukocytes exhibit spontaneous cap formation. This capping is inhibited by cyclic GMP (cGMP) and by cholinergic agonists that increase cellular cGMP generation. The extensive assembly of microtubules seen with the electron microscope in normal human PMN leukocytes incubated with Con A does not occur in PMN leukocytes from CH patients. Incubation of CH PMN leukocytes with cGMP or agents that increase cellular cGMP results in a marked increase in microtubule numbers when cells are exposed to Con A. Because ascorbic acid increases human leukocyte cGMP levels in vitro, CH patients have been treated with vitamin C. Early results in approximately 6 CH patients indicate that vitamin C therapy restores leukocyte function and prevents recurrent infections.

A disease similar to human systemic lupus erythematosus develops in New Zealand black and white (NZB/W) mice; it is characterized by impaired cell-mediated immunity, enhanced humoral immune responses, circulating antibodies to nuclear antigens, and immune-complex glomerulonephritis. Treatment of NZB/w mice with prostaglandin E_1 prevents glomerular deposition of immunoglobulins and complement, the development of proliferative glomerulonephritis, and prolongs their survival.

Prostaglandins and cyclic nucleotides are important regulators of cell function [1,2]. Therefore, these compounds are of interest both to students of cutaneous pathophysiology and to students of cell biology. This paper presents studies on 2 seemingly diverse diseases—Chédiak-Higashi (CH) syndrome and systemic lupus erythematosus (SLE)—that may have in common disordered prostaglandin and/or cyclic nucleotide metabolism and in which the skin is affected profoundly.

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Abbreviations:
cGMP: cyclic GMP
CH: Chédiak-Higashi
Con A: concanavalin A
DE: dermal-epidermal
PGE_1: prostaglandin E_1
PMN: polymorphonuclear leukocytes
SLE: systemic lupus erythematosus

CHÉDIAK-HIGASHI SYNDROME

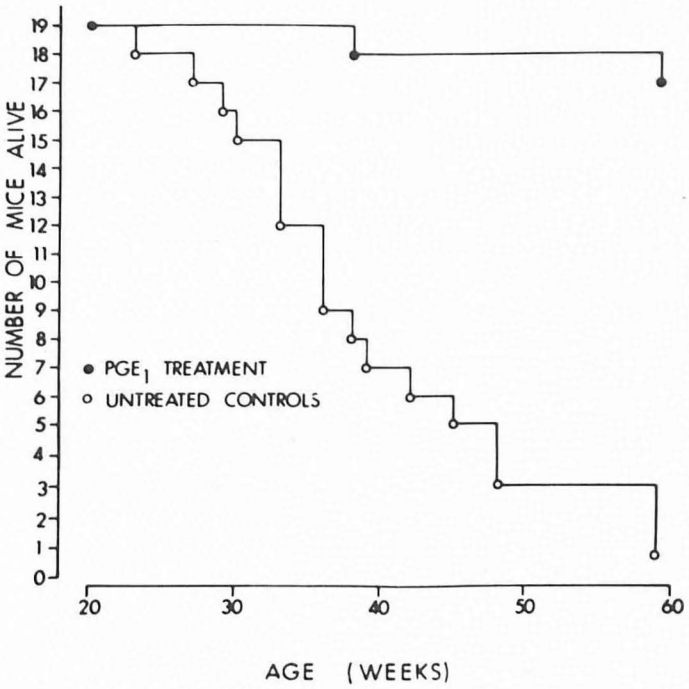
In man the CH syndrome is a rare autosomal recessive disorder characterized by pale skin that sunburns easily, pale or blue-gray hair color, decreased uveal pigment, photophobia, frequent pyogenic infections, and the presence of giant, irregularly shaped lysosomes in most granule-containing cells [3]. An accelerated (lymphoma-like) phase occurs, during which patients have hepatosplenomegaly and lymphadenopathy due to lymphoid and histiocytic infiltrates in these organs [4]. Death usually occurs in childhood as a result of infection or hemorrhage. A similar disorder has been described in mink [5], cattle [6], and mice [7]. Neutropenia, presumably due to intramedullary destruction of cells [8], is common and marrow granulocyte responses are decreased [9]. Chemotactic responses of neutrophils from man [10] and mouse [11] are impaired, but particle uptake by CH neutrophils is normal. The complement of leukocyte lysosomal enzymes is relatively normal [12], although reductions in myeloperoxidase and β-glucuronidase have been reported [13]. These cells exhibit a delay in the killing of intracellular bacteria [14], perhaps as a result of the selective degranulation defect that has been detected in leukocytes from CH patients [12]. A defect in intracellular translocation of lysosomes may also explain the pigment dilution ("partial oculocutaneous albinism") characteristic of the CH syndrome [15]: The lysosomal system appears to be important to the process of pigmentation. Secondary lysosomes (phagolysosomes) are present in the lower epidermis, particularly in the basal cells. They digest phagocytosed melanosomes as melanosome complexes. The transfer of melanosomes from melanocytes to epidermal keratinocytes and to hair cortex cells appears to result from active phagocytosis of melanosomes from the dendritic tips of melanocytes by keratinocytes and hair cortex cells [16–18]. Phagocytosed melanosomes are then dispersed throughout the cytoplasm of the keratinocytes. In the nonexposed skin of Caucasians, melanin is found exclusively in the basal layer, whereas in that of Negroes moderate quantities are seen throughout the epidermis [19]. In Caucasians and Mongoloids the melanosomes in keratinocytes lie aggregated in membrane-bound melanosome complexes (2 to 3 melanosomes), and only a small portion are singly dispersed. In Negroes and Australian aboriginals there are very few aggregates [19–21]. The larger size of Negro melanosomes (0.5 to 0.8 μ vs. 0.3 to 0.5 μ in Caucasians) appears to account for this difference in the phagocytic process [22]. The membrane-bound melanosome complexes contain acid phosphatase and therefore represent phagolysosomes in which melanosomes are being degraded [23]. Thus, melanosomes are less dispersed and are probably removed more rapidly in Caucasians than in Negroes. Similarly, in persons with the CH syndrome, melanosomes remain clumped rather than dispersed throughout keratinocytes and hair cortex cells. The basic defect of the CH syndrome is not known, but it may be caused by abnormal lysosomal membranes. That the giant CH granules of leukocytes stain for acid phosphatase much more rapidly than adjacent normal granules suggests altered membrane structure in CH lysosomes [24]. Recent studies indicate that microtubule function may be impaired in persons with the CH syndrome.

The abnormalities present in the beige mouse, a spontaneous mutant of the C57 black mouse, are considered analogous to

the CH syndrome of human beings [3,11,25]. Polymorphonuclear (PMN) leukocytes from beige (CH) mice exhibit an abnormality of concanavalin A (Con A) distribution that suggested a defect in microtubule assembly in these cells [26]. In lymphocytes [27], virus-transformed 3T3 fibroblasts, and other cells, the disassembly of microtubules by treatment with such agents as colchicine and vinblastine favors the aggregation of Con A into a surface cap [28]; our finding that the PMN leukocytes from normal black mice have a random surface distribution of Con A except after incubation with colchicine (which permits cap formation) is consistent with this fact. By contrast, Con A was capped spontaneously on PMN leukocytes from the CH mice to the same degree as colchicine-treated normal cells. In addition, cyclic GMP (cGMP) and the cholinergic agonists carbamyl choline (carbachol) and carbamyl β-methylcholine (bethanechol), which are capable of raising cellular levels of cGMP [29], normalized the surface distribution of Con A on CH PMN leukocytes and antagonized the colchicine effect on normal PMN leukocytes. We extended these studies to man [30] and showed that an extreme degree of spontaneous Con A cap formation is also characteristic of peripheral blood PMN leukocytes from CH patients. Again, cGMP, carbachol, and bethanechol reduced spontaneous capping.

When normal peripheral blood monocytes are incubated on surfaces in medium supplemented with serum, they mature in 5 to 10 days into typical macrophages, with long cell processes, and a large complement of lysosomal granules [31]. When placed in tissue culture monocytes isolated from the blood of patients with the CH syndrome generate large, irregular granules. When the same cells mature in the presence of carbachol or bethanechol, the proportion of cells containing morphologically normal granules is increased significantly [30]. The addition to human PMN leukocytes of cGMP or agents that enhance cellular concentrations of the nucleotide promotes microtubule assembly in these cells [32]. Thus, CH PMN leukocyte membranes behave like membranes of colchicine-treated normal cells in which microtubules are depolymerized; this observation suggests that microtubule function is impaired in the CH syndrome, perhaps secondary to an abnormality in cGMP generation. Electron microscopic studies [33] confirmed the fact that the characteristic extensive assembly of microtubules observed in normal human PMN leukocytes incubated with Con A [34] does not occur in PMN leukocytes from patients with the CH syndrome. However, incubation of human CH PMN leukocytes with cGMP or cholinergic agonists resulted in a marked increase in the numbers of centriole-associated microtubules when these cells were exposed to Con A [33]. The electron microscopic findings suggest that in CH PMN leukocytes the defect is in the assembly of microtubules rather than in the function of already intact ones.

Microtubules are in a dynamic state of assembly and disassembly, but it is probably in their aggregated state that they exert their influence on cell mechanics [35]. Tubulin, a dimeric protein with a molecular weight of approximately 115,000, has been identified as the major constituent from which microtubules are assembled [36]. Neither synthesis by the CH cell of altered tubulin nor a reduction in the amount of tubulin available appears to explain the inadequate microtubule assembly that we observed in CH mice: CH mouse brain tubulin copolymerizes with rabbit brain tubulin no less than tubulin from normal black mouse brain [37]. In addition, the amounts of tubulin in CH mouse liver, splenic lymphocytes, and granulocytes were comparable to those found in the same tissues in control animals.* Further evidence for a microtubule defect in human CH cells was obtained from studies [38] in which vinblastine induced paracrystal formation (visible by phase contrast microscopy) in only 20% of cells from 4 CH fibroblast



Effect of PGE_1 treatment on survival of female NZB/W mice (treatment begun at 6 weeks). Mice were treated with 200 μg of PGE_1 twice daily (●—●), or with saline (○—○).

lines but in 80% of normal human fibroblasts. Moreover, a reduced association of antitubulin antibody with cytoplasmic filamentous structures (by immunofluorescence), presumed to be microtubules, in confluent mouse CH fibroblasts compared to fibroblasts from normal mice has been observed [33]. CH fibroblasts incubated overnight with 10^{-5} M carbachol showed enhancement of filamentous staining with antitubulin.

Biochemical confirmation of impaired cGMP generation by CH cells has not been forthcoming. However, Boxer et al [39] have shown that the cyclic AMP (cAMP) levels in PMN leukocytes from patients with the CH syndrome are 8 times higher than those found in normal PMN leukocytes, and that ascorbic acid (10 mM) added in vitro substantially reduces cAMP levels in leukocytes from CH patients. Boxer et al [40] showed that incubation of CH PMN leukocytes with bethanechol or treatment of CH patients with this cholinergic agonist corrects defects in PMN chemotaxis and bactericidal activity. Because ascorbic acid increases cGMP levels in human peripheral blood monocytes [41], Boxer and his colleagues administered vitamin C (200 mg/day) to an infant with the CH syndrome. Treatment corrected the PMN functional defects (chemotaxis, bactericidal activity), reduced cellular cAMP to nearly normal levels, and prevented the recurrent infections that had plagued the patient [39]. All responses were reversed after withdrawal of ascorbate. Ascorbic acid treatment has provided symptomatic relief for several other CH patients in North America and Europe.† It is not yet clear whether vitamin C can prevent or alleviate the accelerated, lymphoma-like phase of the CH syndrome.

MURINE LUPUS

In the f_1 hybrid of New Zealand black and white (NZB/W) mice, a disease ("murine lupus") that is remarkably similar to SLE in human beings [42] develops. It is characterized by the appearance of antibodies to nuclear constituents and the subsequent development of an immune-complex-mediated glomerulonephritis [43]. Immunofluorescence studies have shown that host immunoglobulin and complement accumulate in the glo-

* Sherline P, Zurier RB, unpublished data.

† Boxer L, Biggar D, Oliver JM, personal communications.

meruli during the course of both murine [44] and human [45] varieties of SLE. The progress of the disease is variable, but in general immune complexes are deposited rapidly in the kidney during months 4 to 6 [42]. Proteinuria and renal failure then proceed. Deposition of immunoglobulin has been consistently detected at the dermal-epidermal (DE) junction from month 6 on [46,47]. Antinuclear antibodies develop in the majority of mice from months 6 to 9 [48]; circulating antibodies to DNA also develop at that time [49]. Mice generally die between months 6 and 14. The immune status of NZB/W mice can be characterized as an imbalance in which B cell activity and humoral antibody responses are excessive, and T cell activity and cell-mediated immunity are suppressed [48].

Because there was evidence [50–52] that prostaglandin E_1 (PGE_1) could enhance T cell and suppress B cell activity, we treated NZB/W mice with PGE_1. Continuous treatment of female NZB/W mice with pharmacological doses (200 μg once or twice daily) of PGE_1 for 1 year did in fact prevent clinical nephritis and death in these animals despite the fact that treatment did not prevent development of antibodies to nuclear antigens [53]. Thus 17 of 19 treated mice were still alive during week 58 (Figure). In addition, PGE_1 treatment prevented glomerular deposition of immunoglobulins and complement, and development of the proliferative glomerulonephritis characteristic of untreated NZB/W mice [54]. At the DE junction, deposition of IgG was detected by immunofluorescence in 7 of the 12 PGE_1-treated female mice examined. Only 1 animal showed skin deposition of IgM, and none had IgA deposition. At the DE junction in untreated animals, IgG deposition was seen in 10 of 11 mice and IgM deposition was seen in 7 of 11 mice; IgA deposition was seen in only one untreated NZB/W mouse.

The mechanisms whereby PGE_1 exerts its striking effects on murine lupus and the events responsible for renal deposition of immune complexes have not been precisely defined. Complex size and solubility, antigen-antibody ratio, and avidity of antibody for antigen all are important factors [55–57]. It will be necessary to determine whether PGE_1 treatment influences these factors and/or the class of antibodies to nuclear materials that do develop. The age-related loss of responsiveness (^{3}H-thymidine incorporation studies) to phytohemagglutinin exhibited by spleen cells from NZB/W mice [58] is significantly less in cells from NZB/W mice treated with PGE_1 [59]. It is not clear, however, whether PGE_1 in vivo actually enhances cell-mediated immunity or whether preservation of the in vitro response is secondary to good health induced by PGE_1 in some other manner. In many in vitro systems the effects of PGE_1 are due to its capacity to increase cellular levels of cAMP [2]. $PGF_{2\alpha}$ has a minimal influence on cellular levels of this nucleotide. The failure of $PGF_{2\alpha}$ treatment to alter the course of murine lupus [60] suggests that the protection afforded NZB/W mice by PGE_1 treatment may be mediated by cAMP. Whatever the mechanisms be whereby PGE_1 protects NZB/W mice from nephritis and death, their investigation should lead to a better understanding of human SLE.

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